PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 509016	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/NZ2004/000197	International filing date *(day/month/year)* 23 August 2004	Priority date *(day/month/year)* 22 August 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

C07F 9/54 (2006.01) ***A61K 33/42*** (2006.01)

Applicant

ANTIPODEAN BIOTECHNOLOGY LIMITED et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 June 2005	15 December 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NZ/000197

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (under Rules 12.3(a) and 23.1 (b))
- [ ] publication of the international application (under Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[X] the international application as originally filed/furnished

[ ] the description:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: **1 - 12, 18 – 30, 33 – 36, 39 – 42, 45 – 47, 51, 57, 59 – 66 (all partially)**

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*

☒ no international search report has been established for said claim Nos. **1 - 12, 18 – 30, 33 – 36, 39 – 42, 45 – 47, 51, 57, 59 – 66 (all partially).**

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **43, 53 – 55, 80 - 83.**	**YES**
	Claims **1 – 42, 44 – 52, 56 – 79, 84 - 87.**	**NO**
Inventive step (IS)	Claims	**YES**
	Claims **1 – 87.**	**NO**
Industrial applicability (IA)	Claims **1 – 87.**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

D1 WO 2003/016323 A1

D2 KELSO, G. F., et. al. Annals of the New York Academy of Sciences 959:263-74.

D3 JAUSLIN, M. L. el. al. The FASEB Journal 17(13):1972-4.

D4 KELSO, G. F., et.al. The Journal of Biological Chemistry 276(7):4588-96.

D5 US 6331532

D6 SARETZKI, G., et. al. Aging Cell 2:141-3.

Novelty (N) and Inventive Step (IS)

D1 discloses the preparation of certain triphenylphosphonium quinols and quinones falling in the scope of the compounds claimed in claims 1 – 25. While D1 may not specifically disclose that the antioxidant moiety is capable of interacting with mitochondrially active reductants, or that it is a better substrate for reduction of components, such activity appears to be inherent in the claimed compounds. Merely because an applicant has determined a property of a compound, this does not entitle them to claim the compound again, if the compound appears in the prior art, such as D1. The applicant may be entitled to claim the use of the compound to take advantage of the newly discovered property, so long as this property has not been disclosed in the prior art.

D1 provides detailed methods of preparing compounds which are very similar to the compounds prepared in claims 67. A person wanting to prepare compounds having an anion which is non-nucleophilic or exhibits reactivity against the antioxidant, would find D1 highly relevant to the extent that preparing such compounds would be obvious in view of D1 alone. The definition of Z in claim 67 is such that it 'is an anion, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or the compound is in a salt form where the salt is acceptable for pharmaceutical preparation.'. The definition of Z is broad, and is believed to encompass the method disclosed in the prior art. If the compounds of the invention are represented by the compounds of Formula I as denoted in claim 67, then the exemplified compounds of the invention are taken to fall within the scope of Formula I, as well as the methods of their manufacture. Examples of the invention include Mitoquinone-C5 (ie compound 14 in Fig. 2A, where Z is iodide) and Mitoquinone-C15 (ie compound 16 in Fig. 2B, where Z is bromide) –see Example 4. It appears then that the definition of Z is sufficiently broad to include iodide and bromide, as well as other anions which have certain properties. While D1 may not disclose that certain moieties of the prepared compounds are selected on the basis of certain desired properties, it appears that the compounds of D1 either inherently possess these properties, or they are considered to be compounds falling within the claims.

(continued in Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1 – 12, 18 – 30, 33 – 36, 39 – 42, 45 – 47, 51, 57, 59 – 66 are not fully supported by the description. It is quite speculative to attempt to claim all possible compounds (and their uses) based on a desirable antioxidant activity when located in the mitochondria. Some claims (eg claim 29) merely refer to a 'mitochondrial preparation' –the meaning of which is quite unknown, speculative and unsupported. The only support provided for compounds having the alleged effects as claimed, are those having mitoquinone type structures. Hence those claims which do not refer to compounds having a mitoquinone type structure, lack support. Further to the above, the description makes it unclear as to the actual scope of the compounds to be included in the scope of the invention, as opposed to a series of closely related compounds, which presumably are not included in the scope of the invention. It is difficult to ascertain which compounds are comparative examples, and which are examples of the invention, and this is exacerbated by attempting to define the compounds in terms of the expected properties of the compounds of the invention. It would be clearer if the explicit structures of the compounds which are envisaged by the applicant as being those of the invention were revealed. Once the scope of the compounds of the invention have been clearly described and clearly claimed, then it may be possible to better determine the novelty and inventiveness of the claimed matter.

The claims are not fully supported. Claim 47 denotes that the claimed mitochondrially targeted antioxidants are crystalline or solid, but the nature of the exemplified compounds are either not specified, or are a foam or oil. (see compound (2) at p. 50 or compound (16) p. 55) While there is some text suggesting the preparation of crystalline or solid forms of the compounds (p. 5 line 12 – 18), this is not supported in the description. There is no support for a claim to crystalline or solid forms of the claimed mitochondrially targeted antioxidants.

The invention is not clearly described. The premise of the invention appears to be the preparation of certain compounds having a bridge length of C6 or less. (p. 5 line 1 – 11) This has certain advantages. However, the examples include compounds where the chain length is greater than 6 (see compound (16) on pages 54 – 55), and the claims are directed to compounds having chain lengths of greater than 6. (eg. see claims 10 – 14, 52, 53, 58, 67, 72) In view of this inconsistency, the essential features of the invention are not clear. Clarification is sought regarding the essential features of the invention. These should then be reflected in the claims.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

It appears then that the definition of Z does not preclude from its scope, the preparation of compounds of claims 67 – 79. The method of preparation of claims 67 – 79 is not limited to the desirability of having a non nucleophilic or non reactive anion, and besides, the examples of the invention imply quite clearly, that such anions are those which are disclosed in the methods of D1. Therefore claims 67 – 79, at the least lack an inventive step. The methods of preparing such compounds –regardless of the stipulated properties of these compounds- appear to be the same as that disclosed in D1.

Claims 47 – 50 are directed to certain mitochondrially targeted antioxidant compounds in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety. It is agreed that D1 uses a bromide anion which can be said to be nucleophilic. However, it is understood that the bromide anion exhibits no reactivity against the antioxidant moiety, as it is the anion used in the exemplary mitochondrially targeted antioxidant compounds of Example 1 and 2. (see present application compound (2) at p. 49 and compound (16) at p. 55) While it may be that the present claim specifies that the compound is crystalline or solid, the present examples of the invention either denote the isolation of a foam or oil (see compound 16 on p. 55) in the same fashion as D1, or the specification does not specify the form of the isolated compound. (see compound (2) at p. 50) D1 discloses not Mitoquinone-C10 alone, but rather a range of Mitoquinones, which have an alkyl chain length of 2 to 40, having halogen anions, and hence encompasses the antioxidant compounds of claims 47, 48 and 50. Therefore claims 47, 48 and 50 lack novelty and inventive step in view of D1. (see also Observations) D1 does not disclose or suggest the use of the compounds as pharmaceuticals or their use as such, and therefore the present claims to these aspects are novel and inventive in view of D1.

D2 discloses that certain triphenylphosphonium quinols and quinones, falling within the scope of claims 1 – 12 and 47 - 50, prevent oxidative damage in the mitochondria. This is ascertained in part by administering the compositions of the compounds to mice. Therefore the compounds of claims 1 – 12 and 47 - 50 lack novelty and inventive step. D2 does not show or suggest the use of compounds not possessing a decyl carbon chain, and therefore the compounds of claims 13 – 20, the dosage units of claims 53 - 55 and method of claim 43 are novel and inventive. The pharmaceutical compositions of claims 57 – 59 lack novelty and inventive step. There is nothing inventive in preparing dosage units of a pharmaceutically active compound, once the composition is known, and therefore claims 51, 52 and 56 lack inventive step. A skilled addressee would find the preparation of dosage units obvious. D2 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 21 – 28, 45, 60 and 61 lack novelty and inventive step. D2 discloses ubiquinone and tocopherol derivatives which have been determined to be mitochondrially targeted antioxidants. While D2 does not disclose that different mitochondrially targeted antioxidant compounds have different uptake and release, it would be obvious to the skilled addressee that different mitochondrially targeted antioxidants would have differing uptake and release –a skilled addressee would not predict that different such compounds would have the same uptake and release profile. Therefore, in view of D2 it would be obvious to screen for the different uptake and release of mitochondrially targeted antioxidants to determine their differing uptake and release. Therefore claims 29 – 44 lack an inventive step. While D2 does not specifically suggest that the compounds could be used to treat a patient, it would be obvious in view of the results presented by D2, that it could be used to treat a patient, particularly in treating the symptoms of aging. Therefore the method of treatment of claims 46 and 62 - 66 lack an inventive step. D2 does not disclose methods of synthesis, and therefore claims 67 – 87 may be novel and inventive.

D3 discloses that MitoQ –being a compound that falls within the scope of claims 1 – 12 and 47 - 50 is useful in preventing the cell death of fibroblasts from Friedreich Ataxia patients, and shows that such an effect is brought about by the antioxidant activity observed in mitochondria. This confirms their potential in treating Friedreich Ataxia. (see Abstract and Discussion) Therefore the compounds of claims 1 – 12 and 47 - 50 lack novelty and inventive step in view of D3. D3 does not show or suggest the use of compounds not possessing a decyl carbon chain, and therefore the compounds of claims 13 – 20, the dosage units of claims 53 - 55 and method of claim 43 are novel and inventive. Knowing the compounds and their potential to treat Friedreich Ataxia means that preparing pharmaceutical compositions of the same compound, is not inventive. Therefore the compositions of claims 57 - 59, and dosage units of claims 51, 52 and 56 lack an inventive step. D3 discloses that oxidative stress in cells is reduced using compounds falling in the scope of the invention, and therefore the methods of reducing oxidative stress as claimed in claims 21 – 42; 44, 45, 60 and 61 lack novelty and inventive step, as are the methods of therapy as claimed in claims 46, 62 - 66. D3 does not suggest a method of synthesis, and therefore claims 67 - 87 may be novel and inventive.

(continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: previous Supplemental Box.

D4 discloses that MitoQ –being a compound that falls within the scope of claims 1 – 12 and 47 - 50, is an effective antioxidant when located in the mitochondria. This is ascertained in part by administering the compositions of mammalian cell cultures. D4 also discloses the synthesis of Mito-Q. Therefore the compounds of claims 1 – 12 and 47 - 50 lack novelty and inventive step. D4 does not show or suggest the use of compounds not possessing a decyl carbon chain, and therefore the compounds of claims 13 – 20, the dosage units of claims 53 - 55 and method of claim 43 are novel and inventive. The pharmaceutical compositions of claims 57 – 59 lack inventive step, because the preparation of such compositions, in the face of the pharmaceutical benefits of Mito-Q compound revealed in D4, would be obvious. There is nothing inventive in preparing dosage units of a pharmaceutically active compound, once the composition is known, and therefore claims 51, 52 and 56 lack inventive step. D4 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 21 – 42, 44, 45, 60 and 61 lack novelty and inventive step. Therefore the method of treatment of claims 46, 62 - 66 lack an inventive step. D4 reveals methods of synthesis of Mito-Q compounds, and therefore claims 67 – 79 lack novelty and inventive step. Claims 80 – 83 provides a standard method of preparing triphenylphosphine compounds. Once a skilled addressee is made aware of the general structure of the compounds, as is the case in D4 and D5, they would find the method of preparing the compounds obvious. It is a standard technique which would be obvious to the skilled addressee, and furthermore the applicant has not revealed that there was any problem overcome, or particular advantage in preparing the compounds in the manner of claims 80 – 83, and therefore the claimed methods are not inventive.

D5 discloses the synthesis of certain mitochondrially targeted anti-oxidant compounds, known as mitoquinol and mitoquinone, which fall with in the scope of claims 1 – 12 and 47 - 50. This then compromises the novelty and inventiveness of these claims. D5 also discloses the preparation of pharmaceutical compositions comprising these compounds, and this compromises the novelty and inventiveness of claims 57 – 59 as well as the dosage units of claims 51, 52 and 56. (see D5 claims 15 – 22). D5 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 21 – 42, 44, 45, 60 and 61 lack novelty and inventive step. D5 discloses that the antioxidant properties of mitoquinol and mitoquinone may be useful in treating certain disease including Parkinson's disease in whole animals. Therefore the methods of claims 46, 62 - 66 lack novelty and inventive step. D5 reveals methods of synthesis of Mito-Q compounds, and therefore claims 67 – 79 lack novelty and inventive step.

While the citations D2, D3 and D5 may disclose the administration of antioxidant compounds to cells, they are also strongly suggestive and/or indicative that the compounds could be used to treat medical conditions in whole animals. (see D2 p. 265 last 2 lines. When and if the scope of the compounds encompassed by the present invention is clarified (see Certain Observations), then it may be easier to determine if TPMP as noted in D2 impacts on the novelty and or inventiveness of the claims. At present the claims appear to encompass the use of TPMP in whole animals as suggested by D2. See also D3 Abstract which discusses the potential to treat Friedreich Ataxia, a condition suffered by whole animals. Obviously such treatment would involve the whole animal. See also D5 col. 20 lines 8 – 23.) A citation does not have actually exemplify each and every aspect of its disclosure, for it to be a valid disclosure –there may be sufficient discussion and support without exemplification, to enable it to be a citation.